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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,738	11/12/2003	John Hilfinger	TSR-10002/38	7532

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/706,738	**Applicant(s)** HILFINGER ET AL.	
	Examiner Richard Schnizer, Ph. D.	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 November 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *8-24,26,27 and 30*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. NOTE: The proposed proviso "that when A is the C0-C4 alkyl-hydroxy, Q is oxygen" would necessitate new search and consideration.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 8, 13, 14, 17, 20, 23, 24, and 26 under 35 USC 102(b) over Stupp (US 5,932,539).

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:

At page 9 of the response Applicant correctly suggests that the Examiner intended to object to amendments to the paragraph beginning at page 4 line 19 of the specification, and not at page 19 of the specification. Applicant's arguments are persuasive with regard to the issues of cancer, bone diseases, and myasthenia gravis. The specification as filed was drawn to treatment of disease conditions and deficiencies that included all of those recited in the paragraph that followed. After further consideration, treating a "disease condition or deficiency" and treating a deficiency in a disease are considered to be essentially coextensive in scope. However, applicant's arguments with regard to the substitution of "factors" for "disorders" are unpersuasive. As Applicant points out, there are many molecules involved in the clotting cascade. These including clotting factors VIII, IX, X, XI, and XII. However, other molecules are also required that are not referred to as clotting factors, including prekallikrein, high-molecular-weight kininogen, as well as calcium ions and phospholipids. There is no evidence of record that Applicant intended to treat clotting disorders by addressing deficiencies in clotting factors which represent only a subgenus of the molecules involved in clotting. The objection is maintained.

At page 10 of the response, Applicant addresses the objection to the amendment of the specification paragraph beginning on page 9, line 23. Applicant's argument is based entirely on the assertion that "Claim 1 as originally filed taught "R1 is a cholesterol derivative; a C8-C24 alkyl; a C8-C24 heteroatom substituted alkyl wherein

the heteroatom is O, N, or S."" This assertion is incorrect. Apparently Applicant is referring to claim 1 set forth in Exhibit A of the petition filed 4/12/04. However, Applicant's attention is directed to page 3 of the Petition Decision of 7/13/04 which states:

> The application will be processed using pages 14 to 27 of the specification supplied on 12 April, 2004, and the two pages containing Claims 1-7 from provisional Application No. 60/425,379. The other application papers filed on 12 April, 2004, will not be used for processing or examination, but will be retained in the application file.

As a result, claim 1 "as originally filed" is not considered to be the claim listed in Exhibit A of the petition of 12/considered to be claim 1 of provisional application 60/425,379, set forth in Exhibit D of the petition and reproduced below:

> 1. A method for increasing the blood levels of secretable therapeutic proteins in mammals, the method comprising: introducing a formulation into a target cell, the formulation comprising a DNA construct not packaged in a viral particle, wherein the construct encodes a functionally active protein polypeptide that mediates increasing the protein levels in the bloodstream.

Thus Applicant's assertion that R1 is defined in originally filed claim 1 is incorrect and the argument based on the assertion is unpersuasive.

Applicant's assertions at page 10 of the response regarding the objection to claim 18 are moot because the proposed amendment deleting claim 18 was not entered.

Applicant addressed the written description rejection at pages 11-13 of the response. Applicant's arguments based on the assertion that claim 1 as originally filed described R1 as a cholesterol derivative; a C8-C24 alkyl; a C8-C24 heteroatom substituted alkyl wherein the heteroatom is O, N, or S, are unpersuasive the reasons set forth above. Originally filed claim 1 does not support this language. As a result the specification as filed does not support embodiments of 'A' as -sulfonate, -phosphonate,

or targeting ligand groups when A-R1 is other than a cholesterol derivative. Applicant also argues that the specification as filed supported an embodiment comprising R1 as a bile acid, i.e. "a nucleic acid conjugating agent contains a bile acid linked with a polycationic peptide." This is unpersuasive because there is nothing in the specification that correlates R1 specifically with the bile acid that is linked to the polycationic peptide. Applicant argues that since the specification at page 10 describes Z as a polyionic peptide and Y as a linker peptide, that one of ordinary skill would recognize that R1 must comprise a bile acid. This is incorrect. Taking the entire relevant passage into account (page 9, line 15 to page 10 line 7), one of ordinary skill in the art would be more likely to assume that the bile acid is A-R1-Q, because the structure disclosed is A-R1-Q-Y-Z.

Applicants arguments at pages 13-14 regarding the rejection under 35 USC 102 over Gebeyehu are unpersuasive because they are based on proposed amendments that were not entered.

Applicants arguments at pages 14 and 15 regarding the rejection under 35 USC 102 over Stupp are persuasive and the rejection is withdrawn.

Applicants arguments at pages 15 and 16 regarding the rejection under 35 USC 103 over Gebeyehu are unpersuasive because they are based on proposed amendments that were not entered. Also, Applicant's argument that Gebeyehu teaches away from DNA delivery at column 6, lines 37-38 are unpersuasive. This passage merely indicates that compounds other than nucleic acids can be delivered using the disclosed conjugates. Gebeyehu clearly envisions nucleic acid delivery in the abstract

and throughout the application, e.g. at column 5, lines 52-64, and the paragraph bridging columns 11 and 12.

At page 16, Applicant argues that Gebeyehu does not teach or suggest a composition in which the 'A' in the R-A-Z Gebeyehu parlance is oxygen when the 'R' is cholic acid. This is unpersuasive because Applicant is arguing limitations that are not in the claims. Applicant did not explain why this combination of limitations is required and it is not apparent from the pending claims or even the proposed amendment.

Applicant's arguments regarding the rejection of claim 30 over Gebeyehu are unpersuasive because they present no evidence that one of ordinary skill in the art would not have considered it obvious to place the composition of Gebeyehu in some type of container. In fact, it is difficult to imagine how the composition could be used if it is not stored in a container. It would be a matter of routine to store instructions for use together with the composition, however, the courts have found that "instructions for use" limitations do not receive patentable weight because the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, in *In re Ngai* (70 USPQ2D 1862) the court cited the *Gulack* decision stating "[a]s the *Gulack* court pointed out, "[w]here the printed matter is not functionally related to the substrate, the

printed matter will not distinguish the invention from the prior art in terms of patentability." [citation omitted] If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by *Gulack*." The instructions of the instant kits are not considered to distinguish the claimed kits over the prior art because the instructions does not affect the functionality of the product in any way, they merely provide directions for manipulating the product.

Finally, Applicant's arguments at pages 16-18 of the response regarding the obviousness rejection over Gebeyehu in combination with Perrie or Kitadai because are unpersuasive because they are based on proposed claim amendments that were not entered, and because as discussed above, Gebeyehu does not teach away from DNA delivery.

For these reasons the rejections are maintained.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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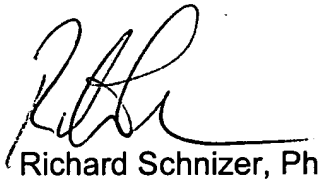

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Art Unit 1635